

AMENDMENTS TO THE SPECIFICATION

Please replace the first paragraph of page 14 of the Specification with the following new paragraph:

The wild-type gene encoding the third intracellular loop of the human alpha-2B receptor molecule is disclosed in GenBank Accession No. # ~~AF316895~~AF005900, the entire disclosure is herein incorporated by reference. As used herein, the term "gene" includes a segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

Please replace the last paragraph on page 57, which continues onto page 58, with the following new paragraph:

The nucleic acid sequence encoding the third intracellular loop of the human alpha-2BAR (GenBank accession # ~~AF316895~~AF005900, SEQ ID NO:1) was examined for polymorphic variation by performing polymerase chain reactions (PCR) to amplify this portion of the cDNA from genomic DNA derived from blood samples. In this application the adenine of the initiator ATG codon of the open reading frame of the receptor is designated as nucleotide 1 and amino acid 1 is the encoded methionine. The human receptor consists of 450 amino acids. For initial examination, DNA from 39 normal individuals was utilized. Two overlapping fragments encompassing the third intracellular loop region were generated using the following primers pairs: fragment 1 (534 bp), 5'-GCTCATCATCCCTTCTCGCT-3' (sense) SEQ ID NO: 13 and 5'- AAAGCCCCACCATGGTCGGGT-3' (antisense) SEQ ID NO: 14 and fragment 2 (588 bp), 5'-CTGATCGCCAAACGAGCAAC-3' (sense) SEQ ID NO: 15 and 5'-AAAAACGCCAATGACCACAG-3' SEQ ID NO: 16 (antisense). The 5' end of each sense and antisense primer also contained sequences corresponding to the M13 forward (5'-TGTAACGACGGCCAGT-3') SEQ ID NO: 17 and M13 reverse (5'-CAGGAAACAGCTATGACC-3') SEQ ID NO: 18 universal sequencing primers, respectively. The PCR reactions consisted of ~100 ng genomic DNA, 5 pmol of each primer, 0.8 mM dNTPs, 10% DMSO, 2.5 units Platinum *taq*TM DNA polymerase (Gibco/ RL), 20 µL 5X buffer J (Invitrogen) in a 100 µl reaction volume. Reactions were started by an initial incubation at

94°C for four minutes, followed by 35 cycles of 94°C for 30 seconds, 58°C (fragment 1) or 60°C (fragment 2) for 30 seconds, and 72°C for one minute, followed by a final extension at 72°C for seven minutes. PCR reactions were purified using the QIAquick™ PCR purification system (Qiagen), and automated sequencing of both strands of each PCR product was performed using Applied Biosystems 370 sequencer using dye primer methods. As discussed, a 9 bp in frame deletion at nucleotide positions 901 to 909 occurring in SEQ ID NO: 2 was detected which resulted in a loss of three glutamic acid residues at amino acid positions 301-303. Thus, this polymorphism was denoted Del301-303. Of note, previous reports have identified this polymorphism (Heinonen, P., Koulu, M., Pesonen, U., Karvonen, M. K., Rissanen, A., Laakso, M., Valve, R., Uusitupa, M., and Scheinin, M. (1999) *J Clin Endocrinol Metab* 84, 2429-2433; Baldwin, C. T., Schwartz, F., Balms, 7., Burzstyn, M., DeStefano, A. L., Gavras, L., Handy, D. E., Joost, O., Martel, T., Manolis, A., Nicolaou, M., Bresnahan, M., Farrer, L., and Gavras, H. (1999) *Am J Hypertens* 12, 853-857). Heinonen et al. refer to the polymorphism as Del 297-299 or DEL 298-300 (which may be a numbering error) while Baldwin et al. refer to it as a 9-base in-frame deletion corresponding loss of 3 glutamic acid residues. No other nonsynonymous or synonymous polymorphisms were identified. PCR amplification of 209 and 200 bp fragments encompassing this polymorphic region allowed screening of additional DNA samples whose genotypes were distinguished by size when run on 4% Nuseive agarose gels. PCR conditions were the same as described above except that buffer F was used with the following primers: 5'-AGAAGGAGGGTGTGTTGTGGGG-3' (sense) SEQ ID NO: 19 and 5'-ACCTATAGCACCCACGCCCT-3' (antisense) SEQ ID NO: 20.